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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/783,248	02/14/2001	Carl P. Decicco	PH-7064 (BMS-0685)	1696
23914	7590	12/16/2003	EXAMINER	
STEPHEN B. DAVIS BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT P O BOX 4000 PRINCETON, NJ 08543-4000			RUSSEL, JEFFREY E	
			ART UNIT	PAPER NUMBER
			1654	
DATE MAILED: 12/16/2003				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/783,248

Applicant(s)

DECICCO ET AL.

Examiner

Jeffrey E. Russel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 5/2/02 and 5/19/03.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-79 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-62 and 65-79 is/are rejected.
- 7) ☒ Claim(s) 3,63 and 64 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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1. The election of species requirement made in the Office action mailed December 12, 2001 is withdrawn.
2. The Sequence Listing filed May 19, 2003 has been approved.
3. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The disclosure is objected to because of the following informalities: At page 3, lines 22 and 30, "octreotide" is misspelled. At page 4, line 18, the beginning parenthesis is unmatched. At page 7, line 11, the second period after "reference" should be deleted. At page 7, line 25, "the growth" should be two words. The status of the U.S. patent applications referred to, e.g., at page 74, lines 8-9; page 86, line 26; and page 92, line 15; should be updated. At page 77, the last line should end with a period rather than a comma. Appropriate correction is required.

4. Claims 6, 7, 9-11, 21, 23, 24, 26, 28-45, 48, 50, 56, 61, 70, and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6, page 135, second paragraph, states that R^1 and R^2 are attached to one another through a nitrogen atom. However, formula (Ia) shows that these two groups are not attached through a nitrogen atom. For analogous reasons, claims 7, 9, 28, and 31 are indefinite. Claim 6, page 135, second paragraph, uses the abbreviations "Ln" and "Ch". However, these abbreviations are not defined previously in the claim, and are not art-recognized standard abbreviations. For analogous reasons, claims 7, 9, 23, 24, and 26 are indefinite. At claim 6, page 135, 12, the second carbon atom in the formula only shows three valences. It is not clear what is attached to the fourth

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valence of the carbon atom. For analogous reasons, claim 28 is indefinite. Claim 6, page 136, lines 1-2, refers to the carbon atom through which R^9 and R^{10} are attached, but ignores the nitrogen atom through which they are attached. Because of this nitrogen atom, any ring system which they form must contain at least 1 heteroatom, and cannot contain as few as 0 heteroatoms as indicated at lines 3-4. For analogous reasons, claims 7 and 28 are indefinite. Claim 7 is indefinite because it does not define the variable R^3 used in formula (Ia). Note that claim 7 is dependent upon claim 1, and not upon claim 6 where the variable is defined. Assuming that claim 7 is amended to recite the same definition for R^3 as appears in claim 6 for the situation where X is C=O, then claim 7 will be indefinite because it defines the variables R^6 and R^7 which are not used in any of the formulas of claim 7. At claim 7, page 138, lines 14 and 21, something is missing from between the two commas after "N". At claim 10, lines 15-20, it is not clear what are the members of the Markush group defining the R variables. Because of the presence of "and" at lines 18 and 20, it is not clear, e.g., if C_1-C_5 alkoxy is the last member of the Markush group and $NHC(=O)R^{17}$ are possible substituents for the C_1-C_5 alkoxy, or if "and" at line 18 should be deleted, making the bond the last member of the Markush group defining the R variables. For analogous reasons, claims 11, 28, and 32 are indefinite. Claim 21 is indefinite because it does not define the variables R^{18} and R^{18a} used at page 149, line 21. Claim 28, line 2, introduces the abbreviations L_n and C_h . In contrast to claims 6, 7, and 9, and to, e.g., page 155, line 5, of the same claim, subscripts are used in these abbreviations. It is not clear if there is any significance in the absence or presence of subscripts in these abbreviations. The use of the subscript "h" at claim 28, line 2, also raises the possibility of confusion with the subscript "h" defined at page 157, line 20. For analogous reasons, claims 30-38 are indefinite. Claim

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terminology needs to be clarified and standardized. Claim 32, lines 3-7, defines a variable W which is not used in any of the formulas of claim 28. It may be that Applicants intended to refer to the variables W^1 and W^2 . Claim 32 is indefinite because it does not define the variable R^{18a} used at page 164, line 1. Further, claim 32 is indefinite because the variable R^{18} , used at page 164, line 1, to define the metal bonding group C_h , is only defined at claim 28 (upon which claim 32 depends), page 157, line 18, as being a bond to C_h . It does not make sense to indicate that the metal bonding group is bonded to itself. Claim 50 refers to a "radiopharmaceutical according to claim 20". However, claim 20 is drawn to a compound, not a radiopharmaceutical. Claims 56 and 61 refer to a compound of claim 47; however, claim 47 is drawn to a radio pharmaceutical, not a compound. At claim 70, line 4, "and" should be changed to "or" so that standard Markush terminology is used. To the extent that claim 79 is attempting to incorporate by reference to the examples, claim 79 is indefinite because it is incomplete. Applicants have not demonstrated that there is no other practical way of claiming the invention, e.g., by reciting the compound names in the claim itself. See MPEP 2173.05(s).

5. Claim 79 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim.

6. Claims 6-9, 17, 22, 28-46, 48, 49, and 65-67 are objected to because of the following informalities: At claim 6, page 134, line 11, "selected" should be inserted after "independently". At claim 6, page 136, lines 8, 11, and 13, "1-4" and "5-7" should be subscripts. Claim 28 contains the same objectionable subject matter as does claim 6. At claim 7, lines 1 and 2, "A compound according to claim 1, wherein" is repeated. At claim 7, page 137, line 3, "selected"

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should be inserted after "independently". At claim 7, page 138, lines 25, 28, and 30, "1-4" and "5-7" should be subscripts. At claim 8, line 8, "1-6" should be a subscript. At claim 9, lines 9 and 11, "5-7" and "1-4" should be subscripts. At claim 17, line 6, "and" should be inserted between "R^{13a}" and "R^{14a}". At claim 17, line 7, the numeral 2's in "OCH₂OCH₂" should be subscripts. At claim 22, page 150, line 5, the numeral 2 in "C₂" should be a subscript. Claim 22 does not end with a period. At claim 29, lines 3 and 8, "1-6" should be subscripts. At claim 30, line 5, "right" should be changed to "ring". At claim 30, line 7, "1-4" should be a subscript. Claim 32 appears to be incomplete, because it ends with "; and" rather than with a period. At claim 33, line 8, "C₂" should be changed to "C₂". Claim 33 does not end with a period. At claim 34, page 165, line 3, "A₅" should be changed to "A⁵". Claim 35 does not end with a period. In the compound named at claim 46, page 171, lines 1-6, the beginning parentheses and brackets do not match the end parentheses and brackets in the compound name. In particular, "2-({2-[(" at line 1 does not match the "amino}ethyl)" and "amino]acetic" at line 5. At claim 65, line 1, "and" should be deleted. The claims should be carefully reviewed for other grammatical and terminology errors, especially the inconsistent and/or improper use or lack of use of subscripts. Appropriate correction is required.

7. The effective filing date of instant claims 1, 2, 4-49, and 51-79 is deemed to be February 14, 2001, the filing date of the instant application. Instant claims 1, 2, 4-49, and 51-79 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/182,627 because the '627 provisional application, under the test of 35 U.S.C. 112, first paragraph, for example, does not disclose targeting moieties which are matrix metalloproteinase inhibitors having a K_i >100 nM (compare page 9, lines 3-12, and claim 1 of

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the provisional application; note also that page 1, lines 1-21, of the provisional application does not disclose compounds with 2-10 targeting moieties and does not disclose the use of chelators); does not disclose R^5 , R^1 , R^2 , R^8 , R^9 , $R^{9'}$, R^{10} , and R^{11} groups which optionally comprise a bond to the chelator; does not disclose R^1 and R^2 forming the ring system of instant claim 6, page 135, lines 4-8; does not disclose the optional R^{27} substituents of instant claim 6, page 135, 27; does not disclose linking groups where W^1 or W^2 are $(OCH_2CH_2)_{76-84}$; does not disclose the second and third formulas of claim 20; does not disclose that the A groups of claim 20 can be N, NR^{26} , NR^{19} , $-S(Pg)$, or a bond to a targeting moiety; does not disclose that R^{23} can be a bond to a targeting moiety; does not disclose the R^{26} group of claim 25 which is a bond to metals in general or which is a hydrazine protecting group; does not disclose the compound recited at claim 46, page 172, line 9; does not disclose the radiosensitizers of claim 59; and does not disclose each of the diseases and conditions recited in instant claims 69-71. Note that unless a claim is limited exclusively to subject matter recited in a parent application, the claim is not entitled to the benefit of the filing date of the parent application. See MPEP 201.11(VI).

The effective filing date of instant claims 3 and 50 is deemed to be February 15, 2000, the filing date of provisional application 60/182,627. Instant claims 3 and 50 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the '627 provisional application because the '627 provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. *Joy Technologies Inc. v. Quigg*, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. *In re Hoeschele*, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. *In re Clinton*, 188 USPQ 365, 367 (CCPA 1976); *In re Thompson*, 192 USPQ 275, 277 (CCPA 1976).

9. Claims 1, 2, 4-46, 55, 60, 62, and 79 are rejected under 35 U.S.C. 102(e) as being anticipated by Carpenter, Jr. et al (U.S. Patent No. 6,656,448). Carpenter, Jr. et al teach the same compounds recited in Applicants' claims 46 and 50, and teach their combination with a pharmaceutically acceptable carrier and a stabilizer and optionally in kit form. See, e.g., column

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20, line 18 - column 21, line 30; column 21, lines 57-60; column 22, lines 5-11; and column 43, lines 52-59. Although Carpenter, Jr. et al intend to complex a diagnostic metal rather than a cytotoxic radioisotope with their chelating groups and intend to use their compounds diagnostically rather than therapeutically, an intended use does not impart patentability to compound claims which are otherwise anticipated by the prior art.

The effective filing date of the subject matter disclosed by Carpenter, Jr. et al and relied upon by the examiner in the above rejection is entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/182,712 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses said subject matter. See, e.g., page 23, line 28 - page 26, line 9; page 76, lines 25-30; and Examples 1-12, 15, and 16. Because the inventorship of Carpenter, Jr. et al is different than the instant application and because Carpenter, Jr. et al has an earlier effective filing date than the instant application, Carpenter, Jr. et al is available as prior art against the rejected claims under 35 U.S.C. 102(e). See MPEP 7606.02(f)(1), Example 2, and MPEP 2136.03(III).

10. Claims 1, 4, 5, 20, 47, 51-56, 60-62, 68-70, 72, and 78 are rejected under 35 U.S.C. 102(e) as being anticipated by Liu (U.S. Patent Application Publication 2002/0004032). Liu teaches compounds comprising macrocyclic chelants linked to a targeting moiety which can be a matrix metalloproteinase inhibitor. Cytotoxic radioisotopes such as ^{186}Re and ^{188}Re can be complexed with the macrocyclic chelants. The compounds can be in kit form including stabilizers and pharmaceutically acceptable carriers. The compounds are used to treat, e.g., cancer, restenosis, diabetic retinopathy, and macular degeneration. See, e.g., paragraphs [0336], [0337], [0404], [0405], [0408], and claim 21.

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The effective filing date of the subject matter disclosed by Liu and relied upon by the examiner in the above rejection is entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/195,234 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses said subject matter. See, e.g., page 40, lines 13-27; page 66, lines 2-10; page 66, line 27- page 67, line 4; and claim 18.

11. Claims 57-59, 65-67, 71, and 73-77 are rejected under 35 U.S.C. 103(a) as being obvious over Liu (U.S. Patent Application Publication 2002/0004032) as applied against claims 1, 4, 5, 20, 47, 51-56, 60-62, 68-70, 72, and 78 above, and further in view of MacPherson et al (U.S. Patent No. 5,646,167) and the European Patent Application 649,658. Liu does not teach combining the compounds with other chemotherapeutic agents or radiosensitizers. MacPherson et al teach combining matrix metalloproteinase inhibitors with other anticancer agents such as methotrexate in order to treat tumors such as human prostate, breast, lung, and colon tumors. See, e.g., column 1, lines 54-55; column 19, lines 57-64; column 20, lines 23-25. The European Patent Application '658 teaches including compounds such as 3-amino-1,2,4-benzotriazine-1,4-dioxide with chemotherapeutic agents in the treatment of solid tumors in order to increase the cytotoxicity of the chemotherapeutic agents. The tumors to be treated include breast and colorectal tumors and lymphomas. See, e.g., page 4, lines 32-38, and claims 1 and 3. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the matrix metalloproteinase inhibitors of Liu with the active agents of MacPherson et al and the sensitizers of the European Patent Application '167 because it is routine in the cancer art to use combinations of anti-cancer agents, because MacPherson et al show that it is known to combine matrix metalloproteinase inhibitors with other known therapeutic agents in

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order to treat cancer, and because the use of multiple agents having different mechanisms of action would have been expected to increase the chances that a cancer would be successfully treated.

12. Claims 3, 63, and 64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 49 would be allowable if rewritten to overcome the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Claims 48 and 50 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, and the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Neither Carpenter, Jr. et al nor Liu is prior art against claims 3 and 50. With respect to instant claims 48, 49, 63, and 64, Carpenter, Jr. et al is limited to diagnostic compositions and does not suggest the claimed cytotoxic radioisotopes which are therapeutic agents. Liu does not teach or suggest the compound structures required by instant claims 48 and 49, and does not teach or suggest the combination of ^{186}Re or ^{188}Re , ancillary ligand, and reducing agent required by instant claims 63 and 64.

The claims of Carpenter, Jr. et al (U.S. Patent No. 6,656,448) have been carefully reviewed but are not deemed to raise any issues of obviousness-type double patenting with the instant claims.

Liu (U.S. Patent Application Publication 2002/0098149) is deemed to be essentially duplicative of Liu (U.S. Patent Application Publication 2002/0004032) applied above.

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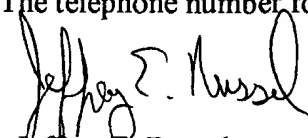
Quirk et al (U.S. Patent Application Publication 2003/0073808) is cited as art of interest, but is not deemed to teach or suggest Applicants' claimed invention. Quirk et al teach compounds comprising a zinc chelator coupled to a matrix metalloproteinase binding region of a TIMP. However, while the MMP binding region is described as binding to matrix metalloproteinases, there is no indication in the publication that the MMP binding region itself has inhibitory activity. Rather, it is the zinc chelator which is described as having inhibitory activity. Accordingly, there is insufficient evidence of similarity between the compounds of Quirk et al and Applicants' claimed compounds to establish prima facie anticipation.

13. In their response to this Office action, Applicants are requested to supply copies of the signed declaration filed July 2, 2001 and the Office action mailed December 12, 2001. Copies of these papers are missing from the image file wrapper, and the examiner would like to ensure that a complete record of the application is present in the IFW.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

PLEASE NOTE: Sometime on or around January 6, 2004, the examiner will be moving to the new USPTO headquarters. At that time, the examiner's phone number will change to (571) 272-0969. After January 6, it is recommended that Applicants attempt to contact the examiner at the new phone number if they are unable to reach him using the old number.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Technology Center 1600 for formal communications is (703) 872-9306; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1600 receptionist is (703) 308-0196.


Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
December 10, 2003